ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure

Building Quality into Clinical Development: ASCEND-HF as a Case Example

Adrian Hernandez, MD and Craig Reist, PhD

Acute Heart Failure: Overlooked

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	Acute HF	Acute MI
Hospitalizations/year	1,000,000	1,000,000
Inpt Mortality	3-4%	3-4%
30-day Readmission	10-20%	6-8%
Guidelines for Risk Stratification	+/-	Yes
Guidelines for Therapy	Yes (ESC/HFSA), 2009 (AHA/ACC)	Yes
Largest Published Randomized Trial	N=4133*	N=41,021
Medline Citations (1965-2010)	1722	120,018

*EVEREST

Acute Decompensated Heart Failure: Past RCTs

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RCT	Intervention	n	Result
FIRST	flolan	471	Higher Mortality
OPTIME	milrinone	951	No Difference/Worse AEs
ESCAPE	PAC	433	No Difference
VERITAS	tezosentan	1760	No Difference
VMAC	nesiritide	489	Improved symptoms, PCWP
REVIVE trials	levosimendan	700	Worse adverse events
SURVIVE	levosimendan	1327	No difference c/w dobutamine
EVEREST	tolvaptan	4133	Modestly improved symptoms
PROTECT	rolophylline	2033	No Difference

Total N: 12,297

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- FDA approved on Aug 10, 2001
  - Intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity

But then…

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Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure

A Pooled Analysis of Randomized Controlled Trials

Jonathan D. Sackner-Bernstein, MD
Marcin Kowalski, MD
Marshal Fox, MD
Keith Aaronson, MD, MS

Context Nesiritide improves symptoms in patients with acutely decompensated heart failure compared with placebo and appears to be safer than dobutamine. Its short-term safety relative to standard diuretic and vasodilator therapies is less clear.

Objective To investigate the safety of nesiritide relative to noninotrope-based control therapies, primarily consisting of diuretics or vasodilators.

Heart Failure

Risk of Worsening Renal Function With Nesiritide in Patients With Acutely Decompensated Heart Failure

Jonathan D. Sackner-Bernstein, MD; Hal A. Skopicki, MD, PhD; Keith D. Aaronson, MD, MS

But then…

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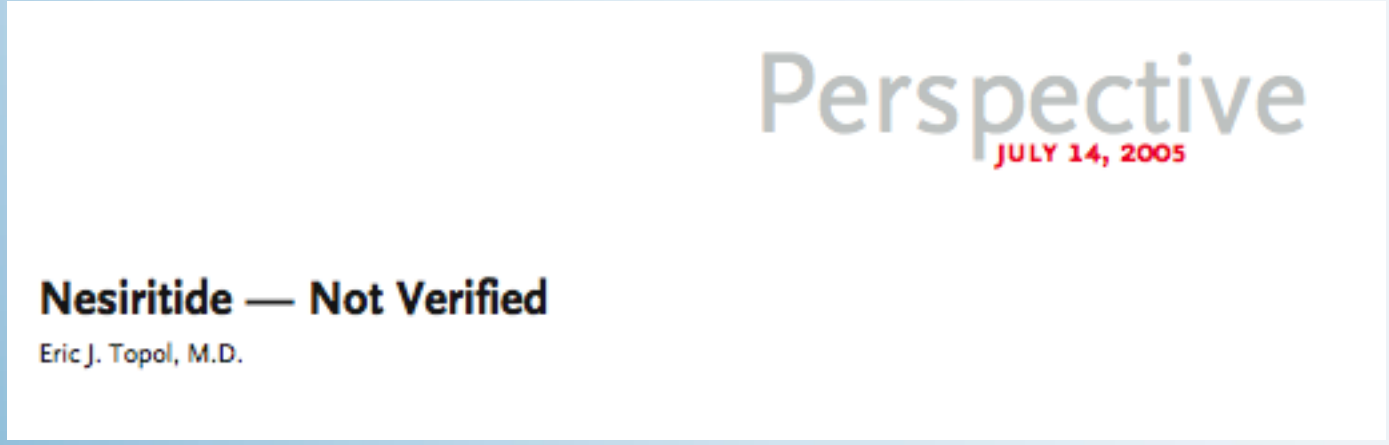

Perspective

JULY 14, 2005

Nesiritide — Not Verified

Eric J. Topol, M.D.

The New York Times
nytimes.com

August 9, 2005

Expert Panel Gives Advice That Surprises A Drug Maker

By STEPHANIE SAUL

Concerns in the Clinical Community

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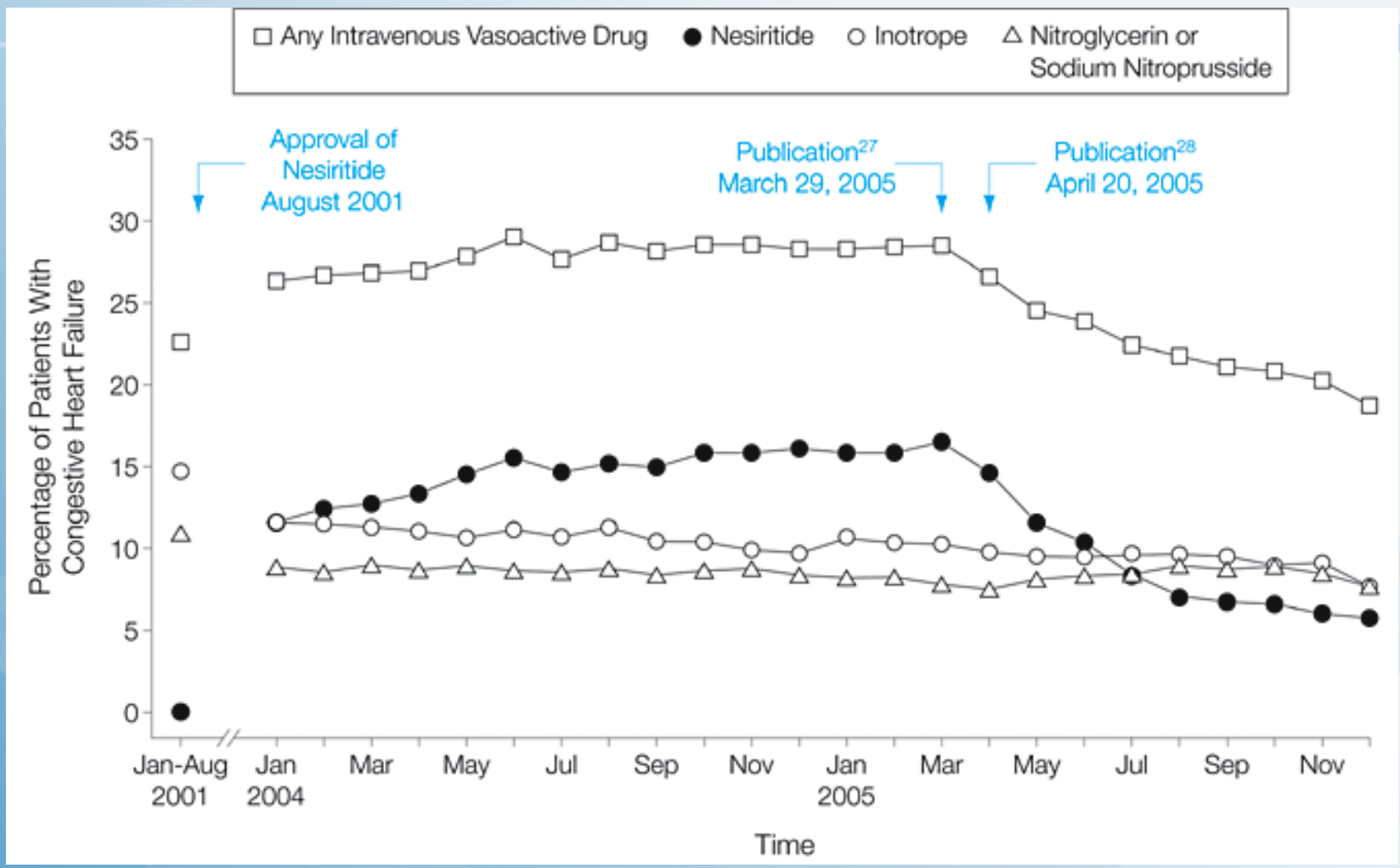

Hauptman, P. J. et al. JAMA 2006;296:1877-1884

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ASCEND-HF: Study Design

Design of ASCEND-HF

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- Investigator independence in context of joint Executive Committee/large Steering Committee
- Large, pragmatic trial model
  - Focused
  - Efficient study design
  - Streamlined procedures
  - Simple follow-up
- Enroll clinical heart failure
- Meaningful outcomes
- ‘Real world’ treatment (standard of care)
- Feasible sub-studies to advance knowledge in acute heart failure

ASCEND-HF: Study Design

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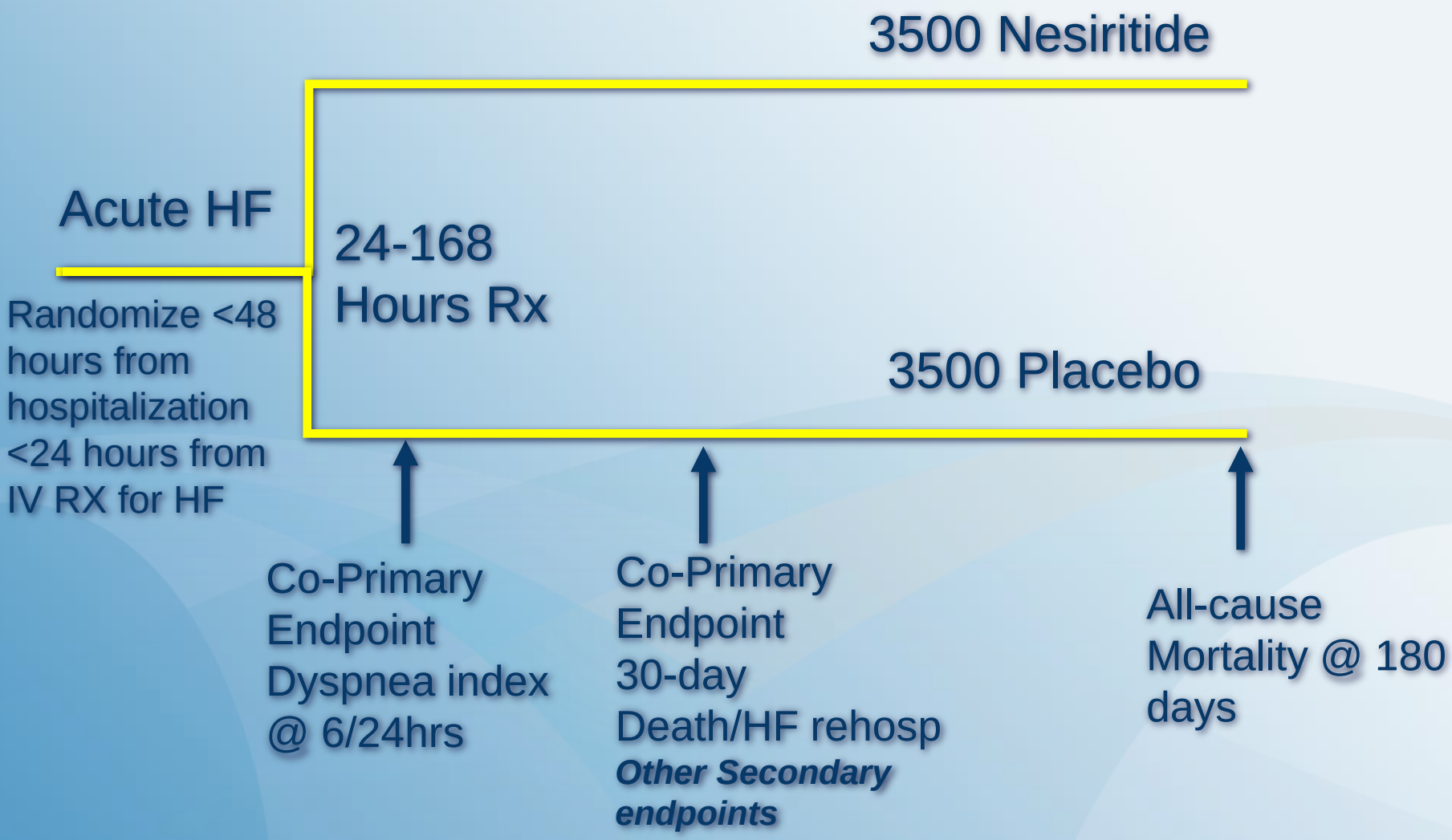

Building in Quality

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- Establish principles for quality operations/data before trial begins
- Integrate principles throughout trial operations
- Communicate expectations to sites and trial teams
- Implement surveillance plans and provide feedback
- Adhere to pragmatic principles
  - Efficient, effective (& hopefully economical)

Guiding Principles: Defining Quality

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1. Have we enrolled the right participants according to the protocol with adequate consent?
2. Did participants receive the assigned treatment and did they stay on the treatment?
3. Was there complete ascertainment of primary and secondary efficacy data?
4. Was there complete ascertainment of primary and secondary safety data?
5. Were there any ***major*** GCP related issues?

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ASCEND-HF: Operational Quality

Did the right participants get enrolled?

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- Design eCRF to capture data to address this question without relying solely on a "did the patient meet criteria" question
  - 88 patients with "no" entered for "Did the subject meet eligibility criteria"
- Monthly review of listings for participants who did not meet ADHF criteria; connect with sites to confirm/correct/re-educate/escalate
  - A majority of the NA participants turn out to be data entry errors that after corrected, fall off the list (41 identified during the first 2 months, 1 remained on the list)
  - In NA, when confirmed not to have met criteria, the sites were re-educated re: ensuring that participants meet criteria prior to enrolling
  - 12 participants from NA confirmed as not meeting criteria (1 site with 2 participants listed, none with more than 2)
  - 31 participants for ROW on the list (3 sites with 3 or more on the list)

Did the right participants get enrolled?

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- On site monitoring of at least 15% of enrolled with at least 1 patient monitored at all sites
  - High enrolling sites received additional monitoring visits
  - Site managers could request out of cycle visit for cause
  - 25% of patients had 100% SDV of the baseline and 30 day visits with 61% of rehospitalized patients having been SDV'd
- Monthly review of operations reports to assess patient demographic data and ensure that comparable patients are being enrolled across geographic regions
  - Lower than expected use of guideline based meds; re-educated sites and issued new CRF query to address
  - Identified need to capture additional data on why sites were not using the bolus; modified CRF to capture reason

Did the right participants get enrolled?

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- Review of Local and Core lab (select countries) BNP samples
  - Identified patients with normal BNP values, looked for site specific trends
    - » - 125 patients with normal values
    - » - 13 sites with >2 patients with normal values
  - One site (7 patients with normal BNPs) was escalated to the Clinical Leadership and Country Steering Committee representative. The group engaged the site PI and re-emphasized the need to ensure that participants enrolled were true ADHF patients. The site agreed to modify their screening to only include higher risk patients. No additional patients with normal BNPs were enrolled post intervention.

Did the participants get the right treatment?

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- Stats monitoring of randomization and kit assignment
  - treatment assignments follow the randomization scheme – no issues identified
  - date falls between 20 May 2007 and date of data transfer to DCRI – no issues identified
  - data fields in the IVRS system match those in the clinical database, e.g. randomization dates, gender, DOB – discrepancies queried and corrected
  - drug treatment codes and dates match those in the randomization file – no issues identified
  - kit numbers in randomization file match those in clinical database – no IVRS/InForm loading issues identified
- EDC query to assess kit dispensed matches kit assigned

Did the participants get the right treatment?

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- Monthly review of operations reports to assess bolus use as well as infusion duration/premature discontinuation/patients not infused and reason
  - Identified "physician decision" as primary reason for bolus omission, added Specify text box to obtain additional data
  - Median infusion duration 42 h
  - Premature discontinuation 7.2% with hypotension primary reason
  - Incidence of patients not infused 134 (1.9%) with hypotension as primary reason 54/134

Did the participants get the right treatment?

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- On site monitoring of 15% of patients enrolled
  - Found 30 protocol deviations related to drug dosing in NA
    - Infusion >24h from same IV bag (9)
    - Wrong weight (5)
- Stats Surveillance Reports to assess site level drug duration
  - Identified 14 (2 NA, 12 ROW) sites that appeared to be administering drug for exactly 24 or 48 hours as opposed to discontinuing at symptom relief
  - Determined that 2 NA were writing orders to run drug for a set time. Re-educated sites with respect to proper discontinuation of drug
  - JNJ GCO following up with ROW sites

Is the primary efficacy and safety data complete + correct?

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- Establish aggressive targets/alarms for data clean
  - >90% clean for baseline, 30 day, 180 day forms
  - No late visits, open/answered queries, missing items > 30 days
- Weekly review of data status and radar reports
  - Sites out of compliance are contacted
- Focused monitoring on at least 50% of re-hospitalized patients
  - Since the primary endpoint includes re-hospitalization for HF, monitoring was weighted to include a high percentage of patients with potential endpoints.

Is the primary efficacy and safety data complete + correct?

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- Monthly review of operations reports aggregate event and safety data with trial leadership/EC/SC
  - Identified lower than expected incidence of use of ACE/ARB, beta blockers and other guideline based meds for ADHF
    - Con-med action plan implemented involving additional database queries to ensure sites were capturing data appropriately as well as additional site education
  - Identified lower than expected event rate in central Europe region and at the recommendation of the Executive Committee stopped enrollment in this region

Is the primary safety data complete + correct?

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- DSMC charter designed to empower committee to use resources (i.e. blinded statistician/independent group preparing data) to assess safety
- Frequent DSMC safety reviews (approx every 1000 enrolled)
  - Committee conducted 6 reviews of the data and recommended continuation of trial at each review

Statistical Surveillance

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- Sites that have randomized at least 10 patients were included
- Key data points such as creatinine values, duration of infusion, and vitals are compared to the regional average to assess expected variability in the data.
- Sites with data at a level of variability that is much smaller than the regional average are flagged.
- A site is flagged if the standard deviation of a variable is less than a fourth of that of all sites in that region.
- The analysis was run several times beginning in 2009, and most recently updated in May 2010.
- Flagged sites were forwarded to JNJ GCO for follow up with the CRA and site PI

Statistical Surveillance

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Variable	Region	Number of sites flagged
Creatinine at end of infusion	Asia	1
	Central Europe	1
BUN/Urea at randomization	Central Europe	3
BUN/Urea at end of infusion	North America	1
	Central Europe	2
Duration of infusion	North America	1
	Latin America	2
	Asia	1

Lost to Follow Up Withdrawn Consent

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- LTFU patients tracked ongoing during study
  - 6 participants LTFU at day 30
- ICF wording in NA to enable use of patient finder service for lost patients
- Report for patients having withdrawn consent enables review for site specific trends and re-education of site with respect to improved screening
  - Globally 30 patients refused treatment
  - Globally 18 WDC for follow up prior to Day 30
- Follow up with site to determine level of withdrawn consent/access to follow up data

Were there any *major* GCP related issues?

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What may be ***"major"***

»Indications that source may not belong to participant

»Participants treated without obtaining consent at all

What probably isn't ***"major"***

»Missing initials on ICF page

»Follow up visits that fall outside protocol window

No Major issues identified

Foundation of Quality Plan

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Global Surveillance is dependent on;

» Site investigators staying current on planned visits and associated data entry and cleaning

» CEC managing rapid processing and adjudication of suspected events

» Statistics/ Data providing regular feedback reports

» Documentation of findings, plans and outcome of intervention

Foundation of Quality Plan – Creating Culture of Currency

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- Sites prefer to work under a structured, mutually understood timeline (avoid ‘firedrills’)
- Identify priorities for cleaning- Oldest to newest
- Provide regular feedback reports to sites on currency and quality of data